REMARKS

This application has been amended in a manner that is believed to place the application in condition for allowance.

Claims 55, 60, 63, and 65-98 are pending in the present application. Claims 55, 60, 63, 65-79, and 81 remain unchanged. Claim 80 has been amended to address a formal matter.

Claims 82-98 have been added. Claims 82-98 are supported generally throughout the specification and in the original claims.

In particular, claim 82 relates to a method of relieving pain in the treatment of Crohn's disease of the anorectum and perianal region. Support for this claim may be found in the present specification, for example, at page 4, lines 3-5 and in Examples 2-3.

Claim 83 is a method of promoting wound healing following a surgical operation to the anorectum or perianal region in the treatment of Crohn's disease of the anorectum and perianal region. Support for claim 83 may be found in the specification at page 4, lines 15-17 and in Example 3.

Claim 84 relates to a method of reducing discharge in Crohn's disease of the anorectum and perianal region. Support for this aspect of the invention may be found in Example 3 set forth in the specification.

Claim 85 is a method of treating Crohn's disease of the anorectum and perianal region using a topical composition comprising about 10 wt% to about 50 wt% of metronidazole. Support for this aspect of the invention can be found in the specification at page 2, lines 14-17.

Claim 86 is a method of treating Crohn's disease of the anorectum and perianal region using a topical composition comprising about 10 wt % metronidazole. Support for this aspect of the invention can be found in the specification, at page 2, line 16.

Claim 87 relates to a method of treating Crohn's disease of the anorectum and perianal region using a topical composition comprising metronidazole as the sole active. Claim 87 is supported by the present specification at page 2, line 25.

Claim 88 is directed to a method of treating Crohn's disease of the anorectum and perianal region using a topical composition consisting essentially of metronidazole and a non-aqueous vehicle. Claim 88 is also supported by the present specification at page 2, line 25.

Claim 89 is a method of treating Crohn's disease of the anorectum and perianal region using a topical composition comprising about 10 wt % metronidazole as sole active. The Examiner's attention is respectfully directed to page 2, lines 16-25 of the present specification for support of claim 89.

Claim 90 recites a method of treating Crohn's disease of the anorectum and perianal region using a topical composition comprising about 10wt % metronidazole wherein the composition has a "fluffy" texture. Support for this aspect of the invention may be found in the present specification at page 2, line 16 and Example 1. Claim 91 is dependent on claim 90 and is also supported by page 2, line 16 and Example 1.

As to the term "fluffy", one skilled in the art would have understood that a composition of metronidazole in white petrolatum would have a gritty texture due to the crystalline nature of the active agent. Even under normal circumstances (i.e. in a healthy human), it would be uncomfortable to apply such a composition to the anorectum and perianal region. However, the application of such a composition to an

inflamed and/or ulcerated anorectum or perianal region would not only be uncomfortable but could also be very painful.

In Example 1, "crude" metronidazole ointment of the present invention is passed through an ointment mill to reduce the particle size of the ointment. The resulting composition has a "fluffy" texture that is smooth and not gritty on application. In this regard, the term is fully supported by the disclosure and definite to one skilled in the art.

Claims 92-98 recite a method of treating a patient having Crohn's disease of the anorectum and perianal region. Support for claims 92-98 may be found generally throughout the specification and in the original claims. In particular, support may be found in the present specification at page 3, lines 8-21 and page 10, lines 14-15

Applicants respectfully submit that no new matter has been added to the disclosure.

Claims 55, 60, 63, 65-67, 68-70 and 76-78 are rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is traversed.

In imposing the rejection, the Official Action alleged that the expression "pharmacologically acceptable derivative" was indefinite. Applicants respectfully submit that the skilled person would have understood that a "derivative" is a chemical compound derived from another chemical compound. If this term were to be used in isolation, then it could conceivably cover any number of different compounds. However, the term has to be considered within the context of the claims. The group of possible derivatives of metronidazole is limited to only those derivatives that are pharmacologically acceptable and in an amount that is "therapeutically effective" in the treatment of Crohn's disease (see e.g., claim 55). Thus, the expression

"pharmacologically acceptable derivative" does not refer to any or all compounds and is definite to one skilled in the art.

Applicants respectfully request that the rejection be withdrawn.

Claims 55, 65-67, 69, 70 are rejected under 35 USC 103(a) as being unpatentable over URBANEK et al. (Vulval Crohns Disease Difficulties in Diagnosis 1996 May 21(3)) in view of ZHOU (CN 1291484A). This rejection is traversed.

The URBANEK publication is directed to the treatment of Crohn's disease. URBANEK discloses that the initial treatment of general Crohn's disease is a medical, successful long-term treatment with oral metronidazole and azathioprine (see page 213, right-hand column, last full paragraph). URBANEK does disclose treating a single patient with a topical application of metronidazole. However, the patient's condition improved "slowly" (see page 211, left-hand column and page 213, right-hand column) and URBANEK does not suggest applying a topical composition comprising metronidazole to treat Crohn's disease in a pharmacologically acceptable non-aqueous vehicle, as claimed.

The Official Action cites to Wenshan ZHOU in an effort to remedy the deficiencies of URBANEK for reference purposes. A full translation of the ZHOU publication is attached.

The composition disclosed in ZHOU is for the treatment of prostate disorders. The prostate is a tubuloalveolar exocrine gland of the male reproductive system. ZHOU discloses a method that comprises applying a composition containing Vaseline, furadantin, and metronidazole directly to the prostate via the anus (see page 2 of the translation attached to this amendment). ZHOU suggests that the combination of furadantin and metronidazole provides a synergistic effect (page 3, lines 15-20).

Applicants respectfully submit that one skilled in the art would have lacked the motivation to combine and modify the publications in a manner that would have resulted in the claimed invention.

Crohn's disease is an inflammatory bowel disease (IBD). It causes inflammation of the digestive tract lining and can lead to abdominal pain, severe diarrhea and even malnutrition (see present specification, page 1, lines 8-15 and page 2, lines 9-10). As noted above, the prostate is an exocrine gland of the male reproductive system.

One skilled in the art would have lacked the motivation to combine and modify these publications as they are directed to treating distinct disorders likely having a different etiology and that affects different parts of the body. Indeed, ZHOU applies a composition comprising metronidazole directly to the prostate via the anus. There is no suggestion that applying such a composition in a different manner (e.g., to a different part of the body or applying the composition after a surgical procedure) to a treat a different disorder that would result in a successful treatment.

Furthermore, Applicants respectfully submit that one skilled in the art would have been dissuaded from using metronidazole to treat other disorders or in the absence of furadantin, as ZHOU discusses the importance of administering furadantin and metronidazole together to obtain a synergistic effect in treating prostate disease.

In view of the above, one skilled in the art would not have considered ZHOU as offering a predictable solution or improvement for treating Crohn's disease. In KSR, the Supreme Court noted that an invention may have been obvious"[w]hen there [was]. . . a design need to market pressure to solve a problem and there [were] . . . a finite number of identified, predictable solutions." 127 S. Ct. at 1742 (tense changes supplied to clarify, as the Court sated and as per 35 U.S.C. § 103, that the obviousness inquiry must rely upon evidence available "at the time" of the invention, see Takeda, 492 F.3d

at 1356 n.2). The Supreme Court's analysis in KSR assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem or pursue potential solutions. Second, KSR presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. See Takeda, 492 F.3d at 1357 ("Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."). Third, the Supreme Court's analysis in KSR presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions," 127 S. Ct. at 1742. In Ortho-McNeil Pharmaceutical, Inc., v. Mylan Laboratories, Inc., 520 F.3d 1358, 1364 (Fed. Cr. 2008), the Federal Circuit further explained that this is "easily traversed, small and finite number of alternatives . . . might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.

Applicants respectfully submit that one skilled in the art would lack the motivation to combine and modify a method for treating Crohn's disease as set forth in URBANEK with a method for treating prostate disease as set forth in ZHOU.

Nevertheless, even if one skilled in the art were to combine and modify the publications, one skilled in the art would not have obtained the claimed invention.

Neither URBANEK nor ZHOU suggests a method of treating Crohn's disease with a topical composition comprising metronidazole and a pharmacologically acceptable non-

aqueous vehicle. In this regard, the proposed combination and modification of URBANEK could not have provided one of the more important benefits of the invention (i.e., systemic side effects associated with treating a patient afflicted with Crohn's disease of the anorectum and perianal region with metronidazole by applying directly to the affected area a topical composition comprising metronidazole in a pharmacologically acceptable non-aqueous vehicle, as claimed. Applicants do not want to be bound by any particular theory but it is believed that by administering metronidazole in this manner, a greater does can be applied to the affected area but a minimal systemic absorption is observed that limits side effects(see present specification, page 6, lines 1-10). Applicants respectfully request that the rejection be withdrawn.

Applicants respectfully submit that claims 68, 78-79, 85-86 and 89-90 are even further distinguishable from URBANEK and ZHOU. URBANEK does not discuss using *any* particular concentration of metronidazole, let alone about 5 wt% to about 15%, about 10 to about 50 wt %, or about 10 wt%. The composition of ZHOU is used to treat prostate disorders. Furthermore, the ZHOU composition contains 20 wt% metronidazole, but does not teach using about 5 wt% to about 15%, or about 10 wt % metronidazole, as claimed. In this regard, Applicants respectfully request that 68, 78-79, 85-86 and 89-90 are even further distinguishable from URBANEK and ZHOU.

The Examiner's attention is also respectfully directed to claim 84, which recites a method of reducing discharge in Crohn's disease of the anorectum and perianal region. Neither publication discloses nor suggests treating a patient suffering for discharge as a result of having Crohn's disease of the anorectum and perianal region

Claims 87, 89, and 97-98 are also further distinguishable from the proposed combination of publications in that URBANEK does not specify the use of metronidazole as the sole active, a topical composition consisting essentially of metronidazole and a

non-aqueous vehicle, or without the use of additional antibiotics and other components. Indeed, the composition of ZHOU contains metronidazole, furadantin, and other compounds such as *andrographis paniculata* (which is a herbal antibiotic).

URBANEK does not specify the use of a topical composition having *any* particular texture, let alone a "fluffy" texture. Likewise, ZHOU does not teach using the composition having *any* particular texture, let alone a "fluffy" texture as recited in claims 90-91. Thus, claims 90-91 are even further distinguishable from URBANEK and ZHOU.

Applicants respectfully request that the rejection be withdrawn.

Claims 60-63, 68, 78-80 and 81 are rejected under 35 USC 103(a) as being unpatentable over URBANEK et al. (Vulval Crohns Disease Difficulties in Diagnosis 1996 May 21(3)) and ZHOU (CN 1291484A) as applied to claims 55, 65-67, 69 and 70 above and further in view of URSING et al. (Metronidazole for Crohn's disease. Lancet. 1975.1(7910)775-777). This rejection is traversed.

The proposed combination of URBANEK and ZHOU fails to disclose or suggest the claimed invention for the reasons noted above.

URSING is cited as evidence that it would have been obvious to one skilled in the art to optimize the amount of metronidazole that is administered to a patient. URSING *discloses treating* patients with Crohn's disease for 4 months to 12 years with metronidazole. However, URSING discloses administering the composition in the form of tablets (see page 776, left-hand column, first full paragraph) with no mention of a non-aqueous vehicle or topical administration. Applicants respectfully submit that the disclosure of URSING is, at best, merely cumulative to that of URBANEK.

Thus, Applicants respectfully submit that URSING fails to remedy the deficiencies of URBANEK and ZHOU for reference purposes, and respectfully request that the rejection be withdrawn.

Claims 76 and 77 are rejected under 35 USC 103(a) as being unpatentable over URBANEK et al. (Vulval Crohns Disease Difficulties in Diagnosis 1996 May 21(3)), ZHOU (CN 1291484A), and URSING et al. (Metronidazole for Crohn's disease. Lancet.1976.1(7910)775-777) as applied to claims 55, 60, 63, 65-67, 68, 69, 70, 78-80 and 81 above, and further in view of GARWIN (US 5248505 A). This rejection is traversed.

The proposed combination of URBANEK, ZHOU and URSING fails to render obvious the claimed invention for the reasons noted above.

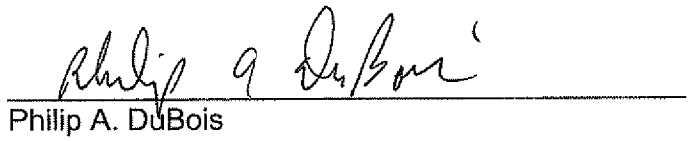
Applicants respectfully submit that GARWIN fails to render the deficiencies of URBANEK, ZHOU and URSING for reference purposes. GARWIN discloses a pharmaceutical composition for treating gastrointestinal distress comprising an effective amount of an antidiarrheal composition (e.g. loperamide, and an antiflatulent effective amount of simethicone) along with methods of treating gastrointestinal distress comprising administering such pharmaceutical compositions. However, there is no recognition of treating Crohn's disease, as claimed.

Applicants respectfully submit that GARWIN cannot remedy the deficiencies of URBANEK, ZHO, and URSING. Applicants respectfully request that the rejection be withdrawn.

The Commissioner is hereby authorized in this, concurrent, and future submissions, to charge any deficiency or credit any overpayment to Deposit Account No. 02-0200 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

BACON & THOMAS, PLLC



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